STORY OF DISCOVERY

Hepatitis B Research Progress: A Series of Fortunate Events

Over the span of a few decades in the U.S., hepatitis B has been transformed from a disease newly infecting 200,000-300,000 individuals annually to one infecting approximately 46,000 individuals in 2006, the most recent year surveyed.[1] This impressive public health achievement can be attributed largely to immunization programs using a safe and effective hepatitis B vaccine, and screening of the blood supply for the virus. Therapy for chronic hepatitis B has similarly improved from a point in time when no effective treatment was available, to the current armamentarium of seven FDA-approved treatment options. These gains in hepatitis B control and care are based on years of careful research, marked by a confluence of serendipity and concerted effort by U.S. and international scientists into understanding the cause and course of hepatitis B, effectively treating it, and preventing its spread. NIH-sponsored research has contributed greatly to advancing knowledge of hepatitis B over the years. This Story of Discovery highlights some of the landmark accomplishments to date in hepatitis B research and their far-reaching impact through translation into improved medical care and public health in this country and around the world.

Silent Disease with a Global Reach

Hepatitis B is an inflammation of the liver caused by infection with the hepatitis B virus (HBV), which results from exposure to an infected person or their blood or blood products. Infection with HBV can result in acute or chronic forms of hepatitis. Symptoms can include fatigue, nausea, fever, loss of appetite, stomach pain, diarrhea, dark urine, light stools, and jaundice (yellowing of the eyes and skin). However, hepatitis B often is a "silent disease," quietly inhabiting the body for several decades before provoking symptoms or progressing to cirrhosis (scarring of the liver that prevents normal function) and/or hepatocellular carcinoma (liver cancer). This delayed appearance of symptoms can hinder efforts to detect the disease at an early stage and to prevent further transmission. Common ways in which HBV is passed on include: from mother to baby at birth; sex without use of a condom; use of tainted needles or tools for injection drug use, tattoos, or body piercing; accidental needle-stick; or sharing a toothbrush or razor with an infected person. Receiving a blood transfusion in the U.S. used to be another common mode of transmission, during the 1980s and earlier, prior to effective screening of donor blood for the virus.

Chronic hepatitis B currently affects an estimated 1.25 million people in the U.S., resulting in approximately 5,000 deaths each year.[1] Recent estimates from the World Health Organization indicate that more than 350 million people worldwide have chronic hepatitis B, out of 2 billion infected with the virus.[2] In particular, individuals from parts of the world where hepatitis B is endemic, such as parts of Asia and sub-Saharan Africa, are at increased risk of developing chronic hepatitis B, which is the leading cause of cirrhosis and hepatocellular carcinoma worldwide. People infected with the human immunodeficiency virus (HIV) are also at high risk of being co-infected with HBV, due to common, bloodborne transmission routes.

Discovery of a Bloodborne Threat to Liver Health

Hepatitis epidemics, which likely included hepatitis B as one cause, have spanned the course of human history, dating back to antiquity and observations on an epidemic of jaundice by Hippocrates. Yet it wasn't until 1883 that a German scientist first described what was later thought to be this particular form of viral hepatitis in a group of people who had developed jaundice after receiving a smallpox vaccine

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prepared from human blood. Similarly, an outbreak of hepatitis-related jaundice affecting approximately 50,000 U.S. Army personnel during World War II was later attributed to HBV infection transmitted through a contaminated yellow-fever vaccine, based on research performed in the late 1980s with support from the Veterans Affairs Medical Center, the NIDDK and the National Cancer Institute (NCI) within the NIH, and the National Research Council.

The infectious agent responsible for these hepatitis outbreaks, the hepatitis B virus, was identified by Dr. Baruch Blumberg while working at the NIH in the 1960s—a discovery that later earned him the Nobel Prize in Physiology or Medicine in 1976. Strangely enough, Dr. Blumberg and his laboratory did not set out to find the virus causing hepatitis B. As part of their research to identify forms of blood proteins that differ across populations or ethnic groups, they were testing blood from hemophilia patients who had received multiple blood transfusions. When proteins in a donor's blood are slightly different from those in a recipient's own blood, the body may mount an immune reaction, including the production of antibodies that stick to the foreign proteins. Thus, the scientists were looking for antibodies in the hemophilia patients as potential markers of differences between their blood proteins and the donors'. In this case, however, the scientists would soon learn that some of the antibodies reflected the presence of a bloodborne infectious agent.

In 1963, Dr. Blumberg and Dr. Harvey Alter identified an antibody in the blood of a patient in New York with hemophilia that reacted against a protein in blood collected from an Australian aborigine. This protein was named the "Australia antigen" or "Au." This finding piqued their curiosity as to why a patient in New York would produce an antibody against a protein found in the blood of an individual so geographically, ethnically, and culturally distinct as an aborigine living in Australia. They went on to test samples from individuals around the globe and found the antigen in some of these as well, more commonly in people who had received multiple blood transfusions or were from Asian or tropical regions.

A clue that the Australia antigen might be linked to liver disease came in early 1966 when Dr. Blumberg's group noted that one patient's blood first tested negative and then positive for the antigen—a shift associated with clinical signs of chronic hepatitis in the form of elevated liver enzymes. Also around this time, one of the technicians in Dr. Blumberg's laboratory developed a case of acute hepatitis, which was accompanied by a positive test for the antigen. Additional clinical studies during the late 1960s in the U.S. and Japan also found hepatitis associated with the Australia antigen. Soon after, blood banks in the U.S. and abroad started screening donors to ensure that this apparent bloodborne cause of hepatitis was not passed on to transfusion recipients.

The Australia antigen was confirmed to be part of a virus causing hepatitis B (now known as HBV) in 1970 by a research group in London that visualized viral particles in blood from patients with hepatitis who had tested positive for the antigen. Once the protein heretofore known as the Australia antigen was revealed to be HBV, scientists realized how the hemophilia patient in New York could harbor antibodies to a protein found in the blood of an Australian aborigine; presumably, both individuals were infected at some point with HBV. In the following years, research would continue to yield illuminating details about HBV. For example, further investigations of the Australia antigen identified it as a protein on the surface of HBV. NIH-supported studies also revealed the distinctive circular shape and other characteristics of the HBV genome. Valuable knowledge of the mechanisms HBV uses for infection and replication, and its overall life cycle, was gained from research in unique animal models

that could simulate human HBV infection, such as ducks, woodchucks, and ground squirrels, as well as from cells grown in the laboratory.

Basic research sponsored by the NIH into understanding HBV components, infection strategy, and resulting disease processes would later prove to be essential as a basis for additional prevention strategies, as well as effective diagnostic and treatment approaches.

Investigations of the disease resulting from HBV infection also showed that chronic hepatitis B could lead also to a form of liver cancer known as hepatocellular carcinoma. For example, in 1981, a study sponsored in part by the NCI of over 20,000 Chinese government workers showed that chronic hepatitis B was strongly associated with development of and death from hepatocellular carcinoma after 5 years. Later, in 2005, the National Institute of Environmental Health Sciences' National Toxicology Program would list the hepatitis B virus as a known human carcinogen in its annual Report on Carcinogens.

Medical Success Story: Effective Prevention of Hepatitis B

Soon after discovery of the Australia antigen, researchers developed tests to detect HBV in blood that could be applied to diagnosis and screening of populations for the infection. Screening of the donor blood supply for the virus had an important impact on reducing disease transmission in patients requiring transfusions. But for prevention in the general population, a vaccine was needed.

Basic research on the natural history of HBV infection led to the preparation in the 1970s and 1980s of the first hepatitis B vaccines based on heat-inactivated and blood plasma-derived viruses. Clinical research on the plasma-derived vaccine conducted with NIH support showed that it was effective at protecting against HBV infection.

Researchers later developed an improved, "recombinant" version of the vaccine by inserting the hepatitis B surface protein gene into yeast or mammalian cells, which facilitated its purification and preparation for the vaccine. These vaccines also protect against infection by the hepatitis D virus, which requires HBV in order to replicate.

Since the establishment in the U.S. in the 1980s of vaccination programs and donor blood screening for hepatitis B, new cases of acute hepatitis B have declined by more than 80 percent.[3] The immunization strategy initially recommended by the Centers for Disease Control and Prevention (CDC) in 1991 entailed universal vaccination of children. In 1992, Federal programs began routine hepatitis B vaccination of infants, and vaccination of adolescents was added in 1995. The vaccine is also currently recommended for individuals in high-risk groups, such as family members of patients with chronic hepatitis B and individuals who inhabit or emigrate from parts of the world with high rates of infection. Worldwide, beginning in the 1990s, the World Health Organization has called for all countries to add the hepatitis B vaccine to their national immunization programs, which presents a challenge in many parts of the developing world. Multi-national public-private partnerships, such as the Global Alliance for Vaccines and Immunization, are working to improve vaccination rates in these areas.

Many Treatment Options for Hepatitis B

Early trials of therapy for hepatitis B focused on the immune-cell chemical interferon. Studies conducted during the 1970s through the 1990s, in the U.S. with NIH support and also abroad, demonstrated the efficacy of treating hepatitis B with interferon, which decreases the stability of HBV genetic material, as well as viral assembly. However, interferon carries potential side effects, including fever, fatigue, headache and muscle aches, and depression. More recently, advances in understanding the viral life cycle and pathogenesis of hepatitis B have paved

the way for identifying new therapeutic agents known as nucleoside/nucleotide analogues, some of which were originally developed to treat HIV infection. These drugs protect against hepatitis B by directly inhibiting replication of HBV through targeting its polymerase enzyme. Currently, seven antiviral drugs are approved by the FDA to treat hepatitis B: interferon-alpha, peginterferon, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. However, no definitive guidance yet exists on the most effective use of these drugs, either alone or in combination. Other issues that remain to be resolved concerning use of these drugs against hepatitis B include how to ensure a lasting response once treatment is stopped and how to avoid the development of viral resistance with long-term treatment, in which the virus mutates over time to escape suppression by the antiviral drug. The drugs also differ in terms of efficacy, safety, likelihood of viral resistance development, method and frequency of administration, and cost. The many HBV types (genotypes) in existence also affect response to therapy and disease progression. New antiviral therapies are currently being tested against hepatitis B in clinical trials.

In addition to pharmaceutical agents, liver transplantation is an effective treatment for individuals with hepatitis B who develop cirrhosis and end-stage liver disease. However, organs for transplant remain in short supply.

To resolve the many issues concerning optimal use of available therapies against hepatitis B, the NIDDK has sponsored several consensus-building conferences that bring together experts in the field to make recommendations based on available evidence. For example, in September 2000 and in April 2006, the NIH sponsored workshops to review current health care practices and develop recommendations for optimal management of hepatitis B. Proceedings from these meetings were published in scientific journals. In October 2008, the NIDDK convened an NIH Consensus Development Conference on Management of Hepatitis B together with the NIH Office of Medical Applications of Research, The Johns Hopkins University School of Medicine, and other entities within the NIH and the Department of Health and Human Services.

The purpose of this 3-day conference was to examine important issues in hepatitis B therapy, including which groups of patients benefit from treatment and at what point during treatment, as well as which groups do not show a benefit. The external experts serving on the conference panel addressed major questions regarding hepatitis B management related to current burden, natural history, benefits and risks of current treatment options, who should or should not be treated, appropriate measures to monitor treatment, and the greatest needs and opportunities for future research on hepatitis B. Additional information on this conference is provided in the accompanying feature on “NIH Consensus Development Conference on Management of Hepatitis B.”

More To Discover Through Research

Despite the impressive scientific gains made over the past decades toward preventing and treating hepatitis B, much remains to be learned about this disease, including details of the disease processes associated with HBV infection, as well as ways to optimize approaches to treatment and control. To further advance knowledge of hepatitis B, the NIDDK is funding the Hepatitis B Clinical Research Network. Established in fall 2008, the Network consists of 12 clinical centers, a data coordinating center, a virology center, and an immunology center. The Network is conducting translational research on chronic hepatitis B, focusing on understanding disease processes and applying this knowledge to more effective strategies to treat and control the disease. Its focus has been informed by the research recommendations of recent NIH-sponsored meetings and planning activities on this topic.

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Through scientific endeavors such as the Hepatitis B Clinical Research Network and investigator-initiated research, conferences, and research planning efforts including the trans-NIH *Action Plan for Liver Disease Research* and the new National Commission on Digestive Diseases' research plan, the NIH is now building upon the extraordinary legacy of past research advances to make additional contributions toward alleviating the burden of hepatitis B, in the U.S. and throughout the world.

[1] *http://www.cdc.gov/hepatitis/PDFs/disease_burden.pdf*

[2] *http://www.who.int/mediacentre/factsheets/fs204/en*

[3] *http://www.cdc.gov/ncidod/diseases/hepatitis/resource/PDFs/disease_burden.pdf*

Additional information on hepatitis B and research progress on this disease is available through the following NIH resources:

- NIH Fact Sheet on Hepatitis B, available at: *http://www.nih.gov/about/researchresultsforthepublic/HepatitisB.pdf*
- Materials for the public provided by the National Digestive Diseases Information Clearinghouse (*http://digestive.niddk.nih.gov/index.htm*), including the brochure "What I Need to Know About Hepatitis B," available in electronic or printed form.